Atty. Docket No.: VI/99-020

#5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
DVORSKY et al.	)	Art Unit: 3737
	)	
Serial No.: 10/060,561	)	
	)	
Filed: January 30, 2002	)	Examiner: Barry Pass
	)	
For: APPARATUSES, SYSTEMS AND METHODS FOR EXTRAVASATION DETECTION	)	

DECLARATION UNDER 37 C.F.R. § 1.131
TO OVERCOME CITED U.S. PATENT REFERENCE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Declaration is being filed to establish completion of the invention of Claims 7, 11, 16, 18 and 23 in this patent application in the United States on a date before February 2, 2001, which is the earliest priority date of cited U.S. Patent Application Publication No. 2002-0172323 to Karellas et al. ("the Karellas patent").

To establish the date of completion of the invention of Claims 7, 11, 16, 18 and 23 in this patent application, the following document is submitted herewith as evidence: "Extravasation Phase 2 Final Report" (including experimental set-up and results, and photographs).

From the enclosed document, it can be seen that the invention of Claims 7, 11, 16, 18 and 23 in this application was made at least by the date of June 8, 1999 (i.e., the date of the report), which is a date earlier than the earliest priority date of the Karellas patent.

This Declaration is made and executed by Mr. Chad Bouton, a named inventor of this application and the author of the accompanying "Extravasation Phase 2 Final Report."

This Declaration is being submitted in response to the rejection of Claims 7, 11, 16, 18 and 23 based on the Karellas patent in the Office Action mailed on June 3, 2003.

As a named inventor signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Name of Inventor:	Chad E. Bouton
Signature of Inventor:	Chad E. Bouton
Date:	October 1, 2003
Citizenship:	United States
Residence:	Delaware, Ohio
Post Office Address:	312 Pecan Court Delaware, OH 43015

MEDICAL PRODUCTS

Extravasation

Phase 2 Final Report

for Medrad Incorporated

C. Bouton

June 8th, 1999

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Introduction and Phase Summary

Battelle
The Business *of* Innovation

MEDICAL PRODUCTS

Introduction

- Review Radioactive Source-Detector Concept

- Phase 1 key objectives

  -CM radioactive photon absorption characteristics
    - Iodine concentration
    - Shape

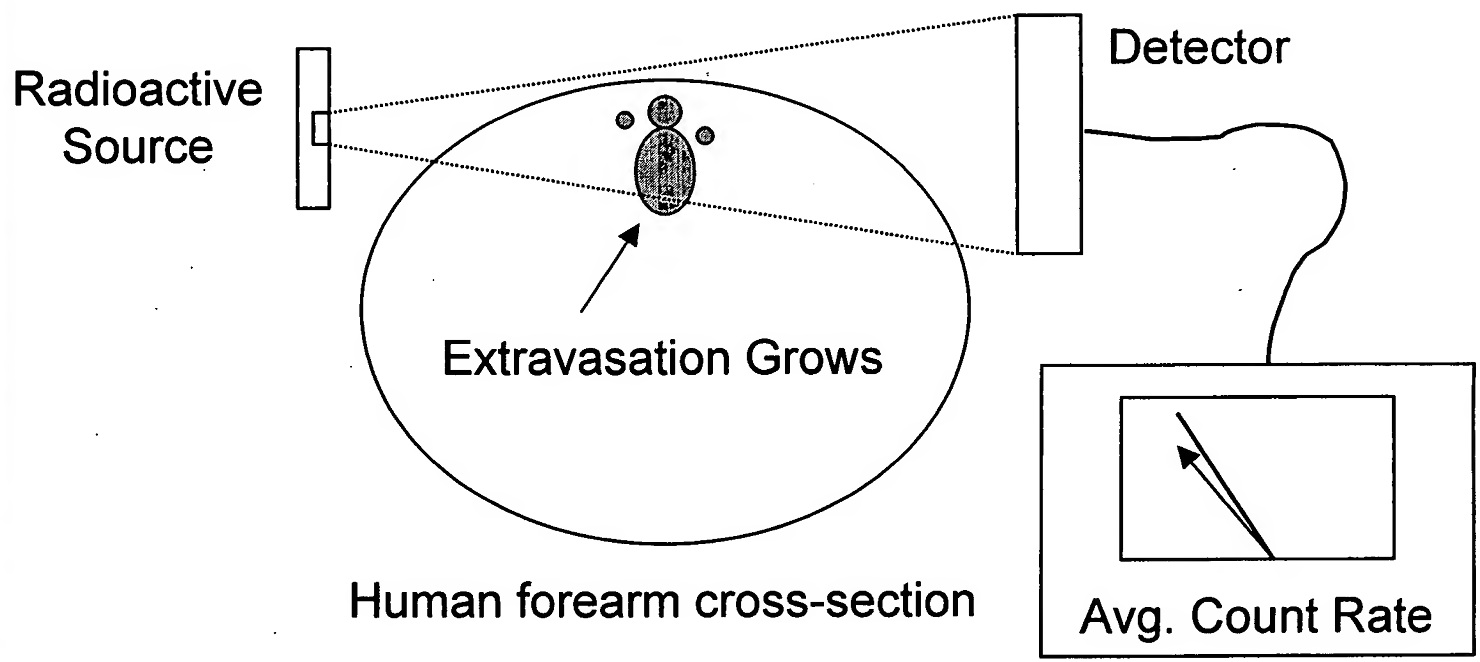
  -Basic response time predictions

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Introduction

- Review Radioactive Source-Detector Concept



Battelle
The Business of Innovation

MEDICAL PRODUCTS

Introduction

- Review Radioactive Source-Detector Concept

- Phase 1 key objectives

  -CM radioactive photon absorption characteristics
  Iodine concentration
  Shape

  -Basic response time predictions

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Introduction (cont.)

- Phase 2 key objectives

  -Detector efficiencies (GM and CZT)

  Impacts patient dose

  -Improve phantom (size, skin, add bone)

  -Investigate single and complementary (dual) source-detector (S-D) pairs

  Increase sensitivity / decrease false alarms

  Dual: decrease patient arm motion sensitivity

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Introduction (cont.)

- Phase 2 key accomplishments

  -Detector efficiencies (GM, CZT, Xe, Si)

  -Investigated alternative detector technologies
    Xe, Si diodes, aSe
    Scintillating fiber: Battelle-managed Pacific Northwest National Laboratory (PNNL)

  -Improved phantom (size, skin, bone)

  -Verified water absorbs and scatters radiation similarly to soft tissue

  -Used energy spectral analysis

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Introduction (cont.)

- Phase 2 key accomplishments (cont.)

  -Two new concepts for modes of detection

  X-ray fluorescence

  Scatter mode (backscatter allows co-located S-D)

  -Discovered using Iodine-129 as a source may be superior to using Americium-241

  Completed simple model with energy variable

  Discovered optimal energy range

  Searched through Nuclide database

  -Investigated source-detector *arrays* (fundamental)

  Increased sensitivity / decreased false alarms

  Decreased S-D motion sensitivity

  Enlarged search volume

MEDICAL PRODUCTS

Introduction (cont.)

- Phase 2 key accomplishments (cont.)
  - -Determined key system performance factors
  - -Measured doserate and predicted patient dose
  - -Completed S-D motion experiment to determine level of importance
  - -Completed initial evaluation of energy windowing effectiveness with Am-241 (should try Co-57)

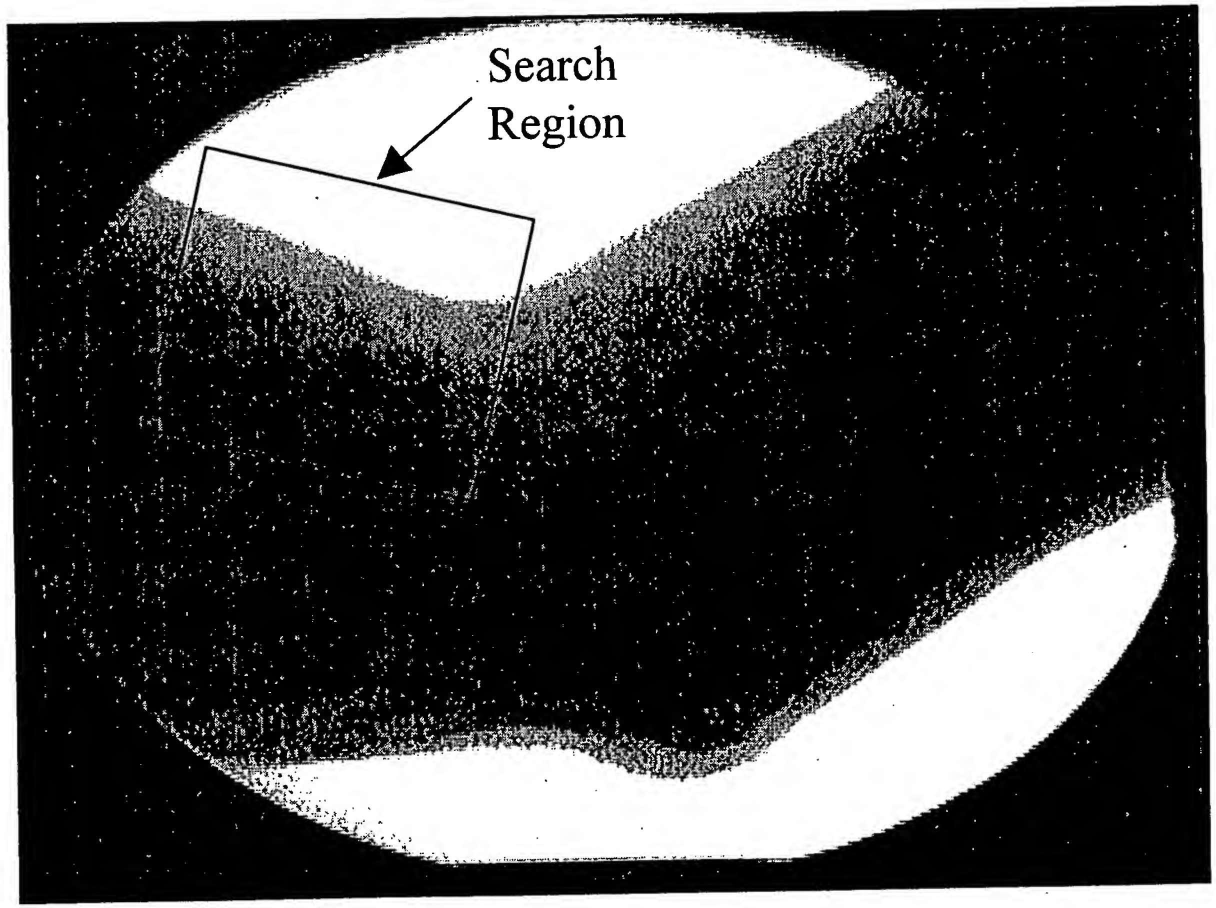
MEDICAL PRODUCTS

Detector Efficiencies

Detector Type	Manufacturer, Model	Shape, Active Area Size	Cost/Qty.	Counting Efficiency for 60 keV Gammas	Information Source
Geiger-Mueller Tube (#1)	LND, 7311	Round, 44.5 mm diam.	$75/1	1%	Determined Experimentally at Battelle
Geiger-Mueller Tube (#2)	LND, 7311	Round, 44.5 mm diam.	$75/1	1%	Determined Experimentally at Battelle
CZT	eV, custom	Round, 14.7 mm diam	–	95%	Determined Experimentally at Battelle
Xenon Gas Filled Proportional Counter	LND, 4312	Round, 44.5 mm diam.	$425/1	10%	Determined by Manufacturer
Silicon (300 μm thick)	Detection Technology, XRB 50s-CB	5x5mm	$69.80/1 $22.30/1000	2%	Determined by Manufacturer

MEDICAL PRODUCTS

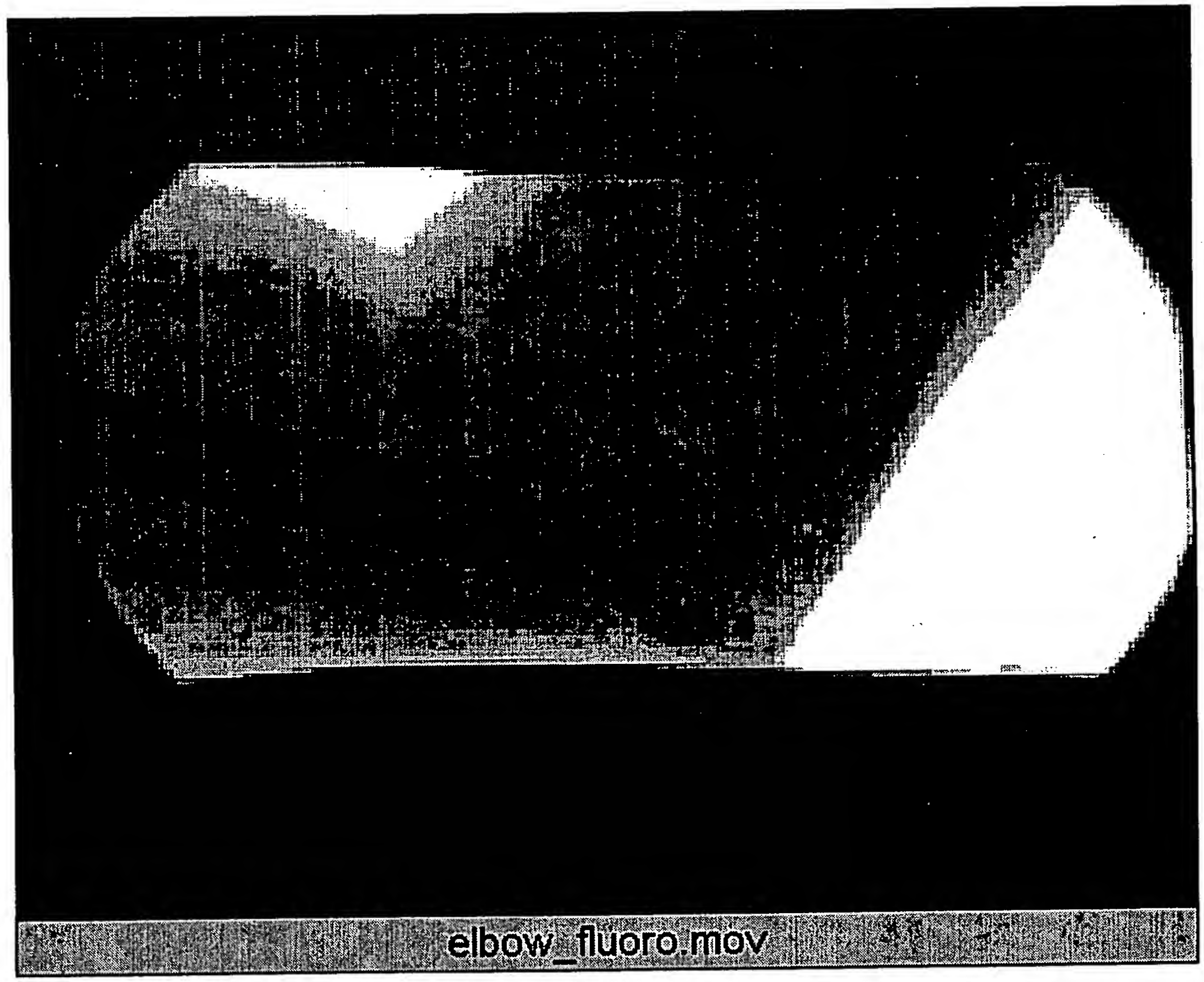
Improving the Phantom



Fluoroscope Image of Human Elbow

MEDICAL PRODUCTS

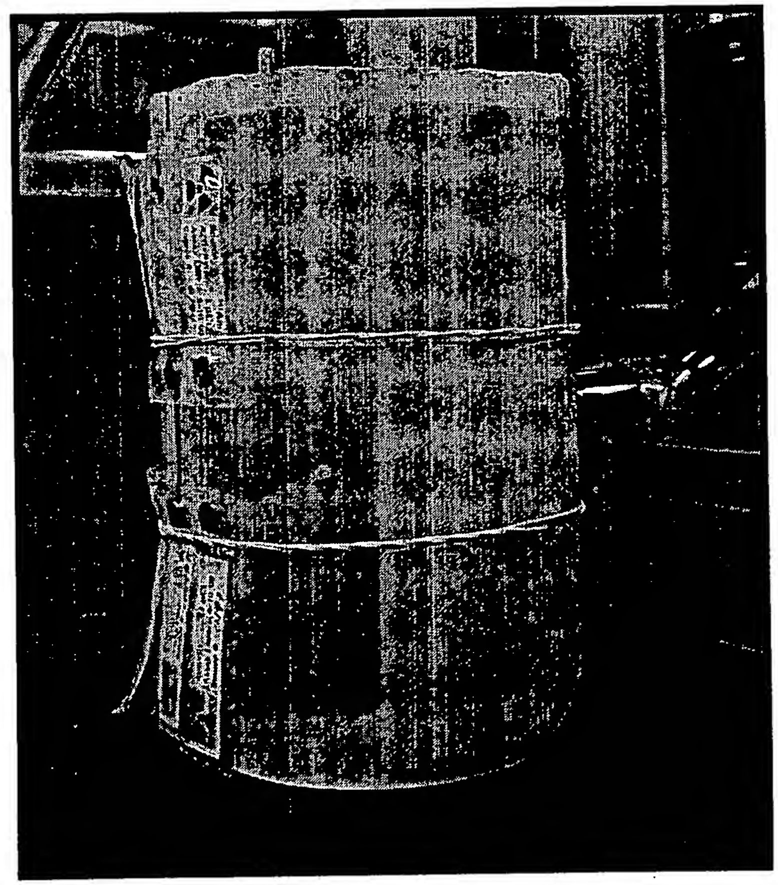
Improving the Phantom (cont.)



MEDICAL PRODUCTS

Improving the Phantom (cont.)

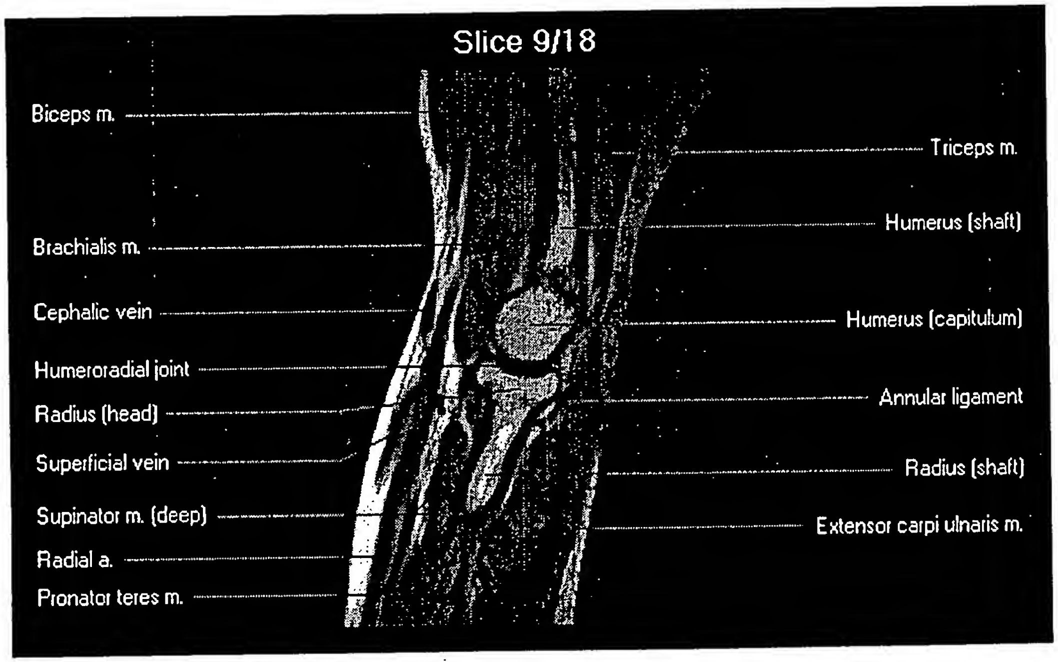
- Larger (9cm diam.)
  - 75th % male elbow bend
  - >100th % female
  - >90th % total pop.
- Better skin
- Bone included
  - epoxy resin
- Balloon used



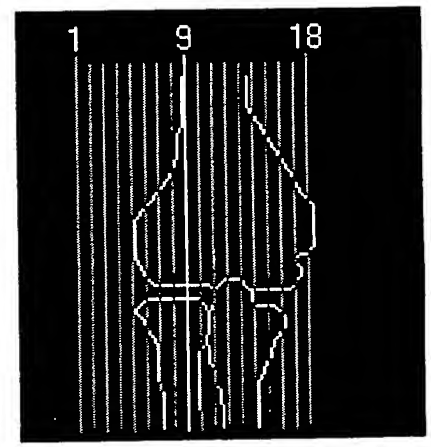
Battelle
The Business of Innovation

Improving the Phantom (cont.)

Sagittal - Medial (Inside of Arm) View



Cross-Section Location
Anterior (Front) View

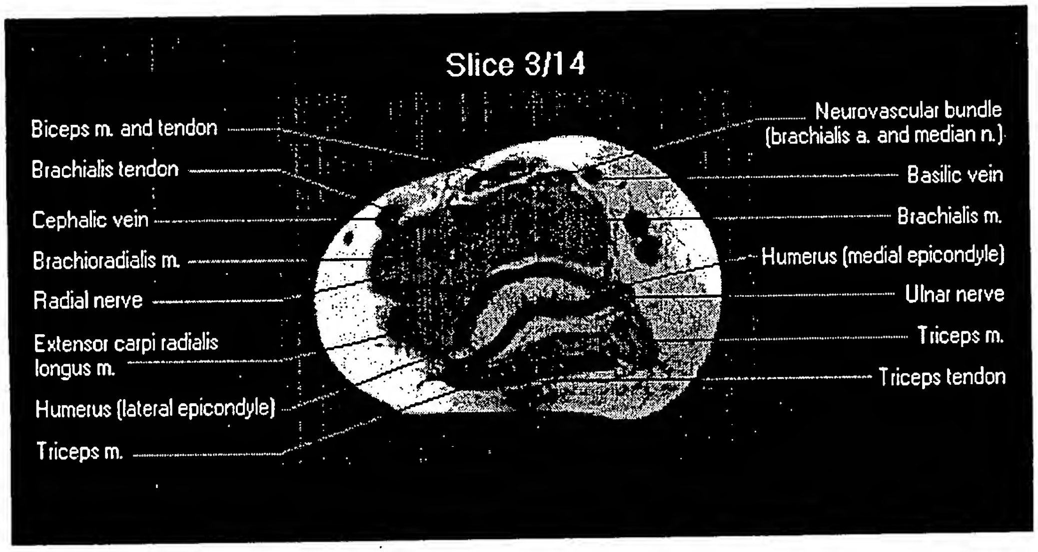


MEDICAL PRODUCTS

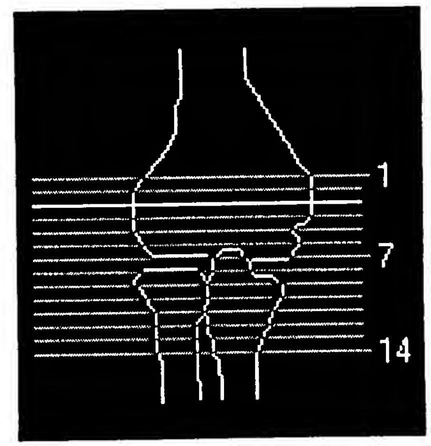
Battelle
The Business of Innovation

Improving the Phantom (cont.)

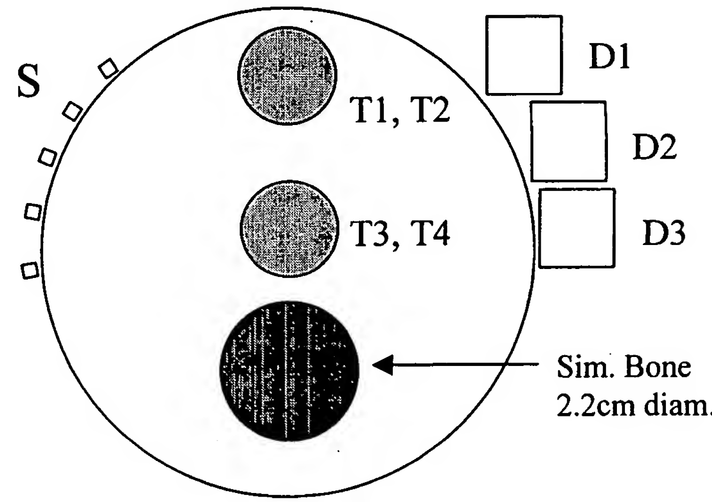
Transverse - View from Distal (Hand) End



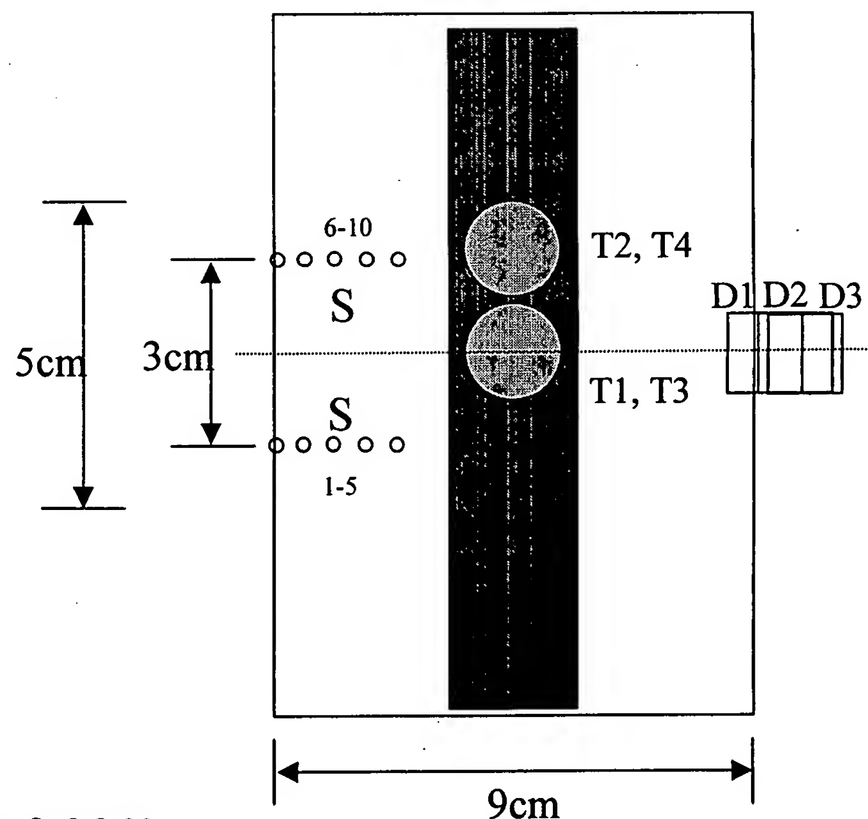
Cross-Section Location
Anterior (Front) View



Improving the Phantom (cont.)

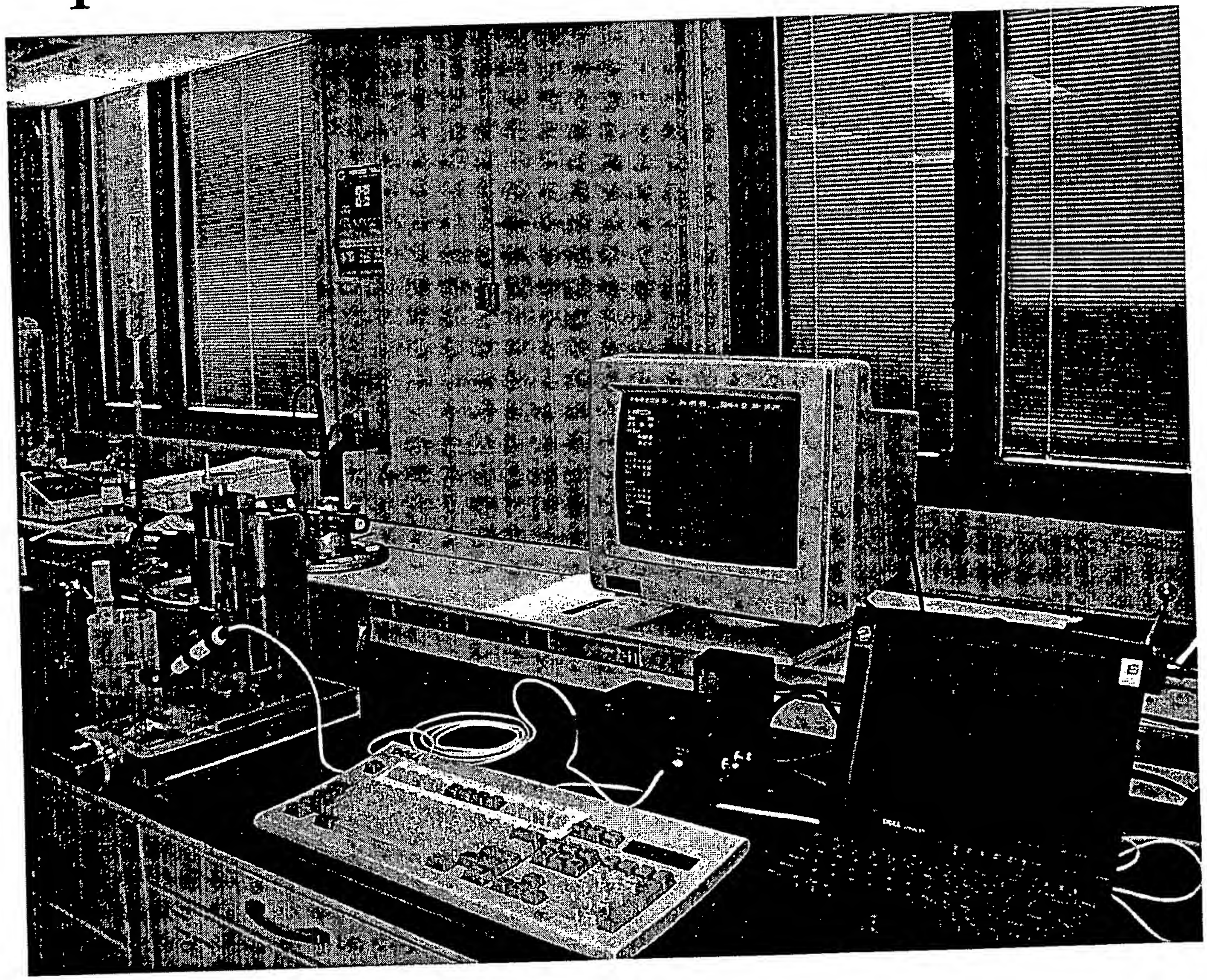


S = Source
D = Detector
T = Target



MEDICAL PRODUCTS

Experimental Setup

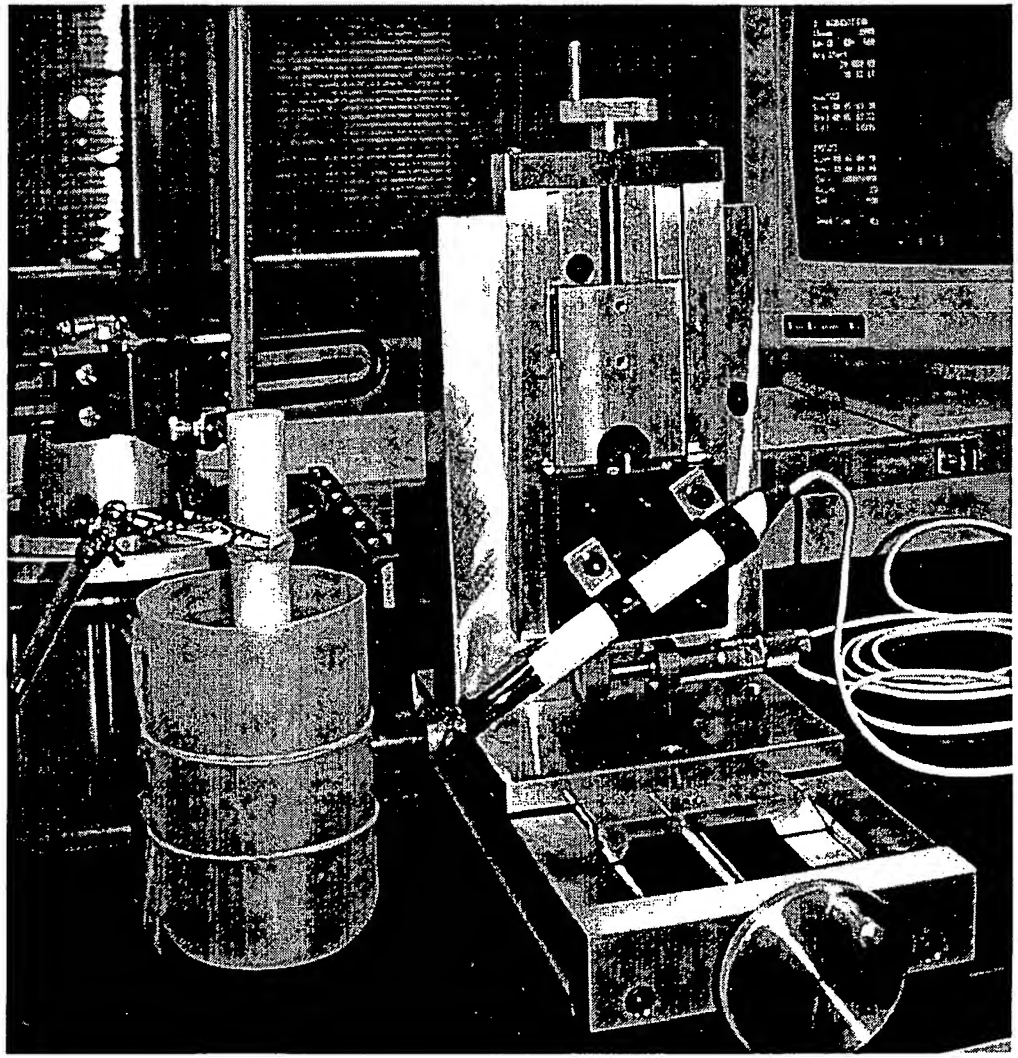


Medrad Extravasation Phase 2, 6-8-99

Battelle
The Business of Innovation

MEDICAL PRODUCTS

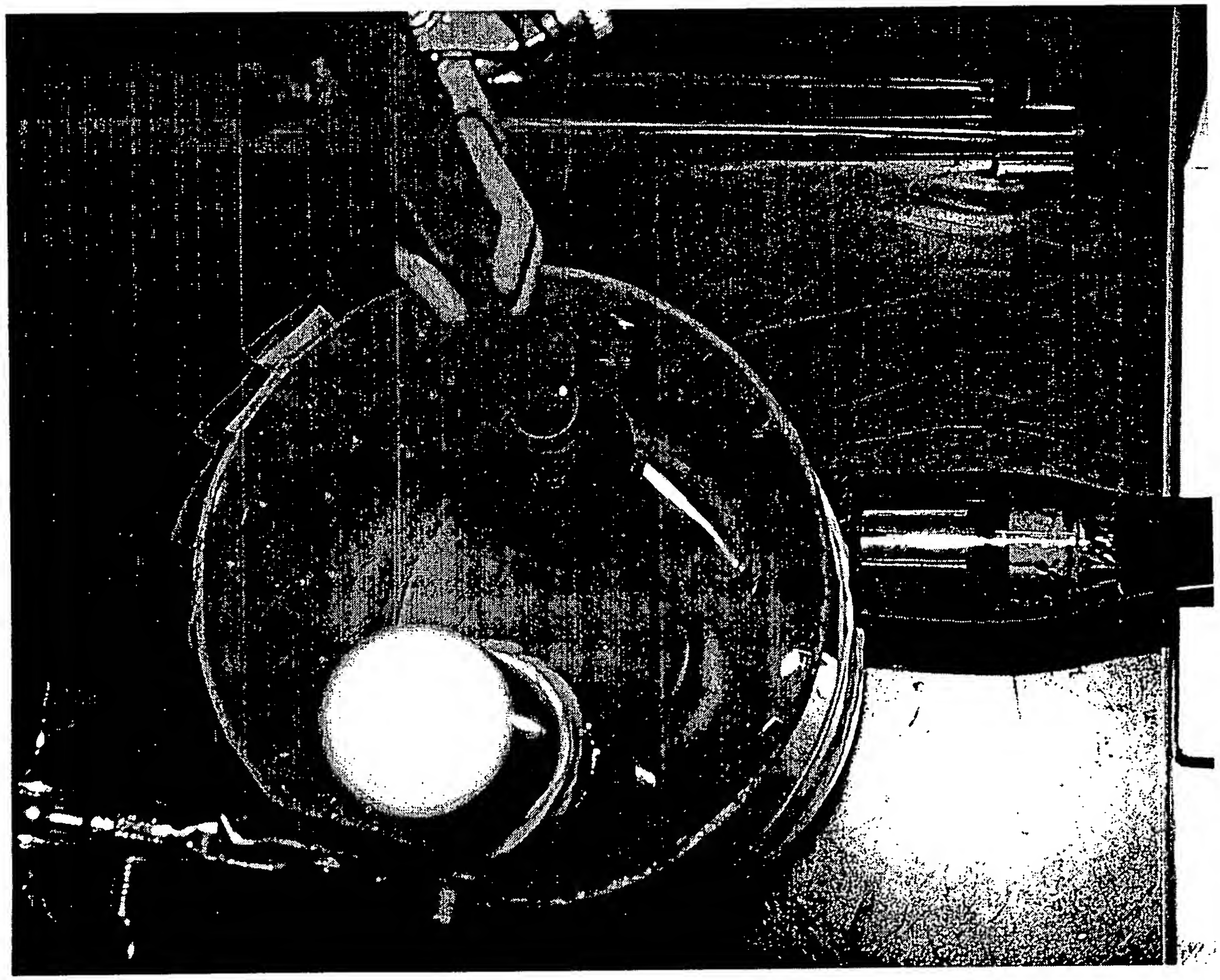
Experimental Setup (cont.)



Battelle
The Business of Innovation

MEDICAL PRODUCTS

Experimental Setup (cont.)



Battelle
The Business of Innovation

MEDICAL PRODUCTS

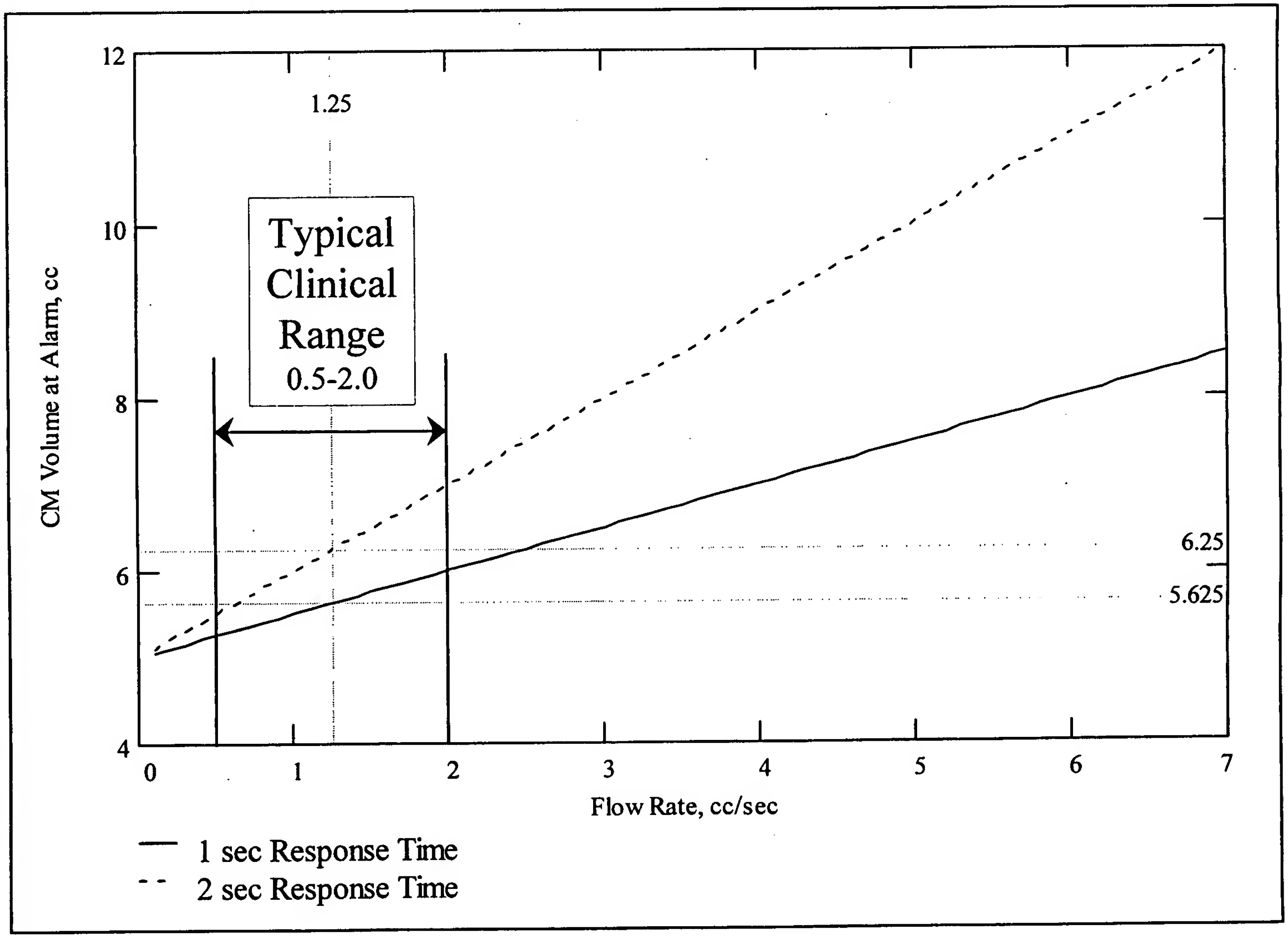
Performance Goals and Criteria

- Detect $\leq$5cc of CM (370 mgI/mL)
- Response time of 2 sec or less
- At what volume of CM does the system alarm? (Function of ***leak*** flow rate)

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Performance Goals and Criteria (cont.)



Battelle
The Business of Innovation

MEDICAL PRODUCTS

Performance Goals and Criteria (cont.)

- Dose to patient is small fraction of CT dose
- False positive (alarm) probability of 1%
  - -System alarms in about 1 out of 100 procedures (20 min)
  - -Competition is at 3% false alarm probability
- False negative probability of 1%
  - -No alarm occurs when it *should*
  - -Low false negative prob. improves response time validity

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Experiment and Analysis Steps

- Acquire accurate Baseline Counts (balloon deflated) for 3 detector and 4 target locations
- Acquire accurate Target Counts (5cc of CM added to balloon via syringe) for 3 detector and 4 target locations
- Determine Percentage Count Reduction (PCR) for 16 configurations ([3 individual detectors + 1 sum] x [4 target locations])

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Battelle
The Business of Innovation

Experiment and Analysis Steps (cont.)

- Calculate required PCR margin = 7% (S-D motion margin + Baseline & Target Count accuracy - i.e. confidence interval)
- Determine which target-detector configurations satisfied PCR margin
- Measure source dose rate and predict patient dose from source array
- Complete S-D motion experiment
- With and without simulated bone

MEDICAL PRODUCTS

Experiment and Analysis Results

- Satisfied detection margin (7%) for 13 of the 16 target-detector configurations (two of the detector configurations worked for **all 4** target locations)

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Experiment and Analysis Results (cont.)

Percentage Count Reduction (PCR), %				
Target Location	**D1**	**D2**	**D3**	**D1+D2+D3**
T1	38, 43[3]	21, 22[3]	9, 10[3]	23, 25[3]
T2	14, 17[3]	8, 7[1,3]	6[1], 9[3]	9, 12[3]
T3	7[1]	16	25.8, 26.3[2]	15
T4	4[1]	9	12	8

[1] Less than or equal to total margin for measurement error (2-4%) and source-detector motion (3% for 2mm case).
[2] Simulated bone excluded from phantom.
[3] Narrow energy window used around photopeak to increase PCR.

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Experiment and Analysis Results (cont.)

- Extensive statistical analysis showed system can achieve stipulated response time and false positive/negative probabilities (see *Phantom Data and Primary Analysis*)
- Dose measurements and data analysis shows if CZT (highly efficient detector) is used the required dose to patient is...

Battelle
The Business *of* Innovation

MEDICAL PRODUCTS

Performance Results (cont.)

Calculated Dose for 20 Minute Exposure, Units: % of Brain CT Dose

Target Location	D1	D2	D3	D1+D2+D3
T1	0.24, 0.32[3]	0.28, 0.38[3]	0.32, 0.42[3]	0.22, 0.26[3]
T2	0.30, 0.38[3]	0.32, 0.42[3]	0.32[1], 0.42[3]	0.26, 0.30[3]
T3	0.32	0.30	0.29, 0.28[2]	0.24
T4	0.32	0.32	0.32	0.26

[1] May be higher if new source-detector configuration is used to increase PCR.
[2] Simulated bone excluded from phantom.
[3] Narrow energy window used around photopeak to increase PCR.

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Performance Results (cont.)

Dose references for comparison:

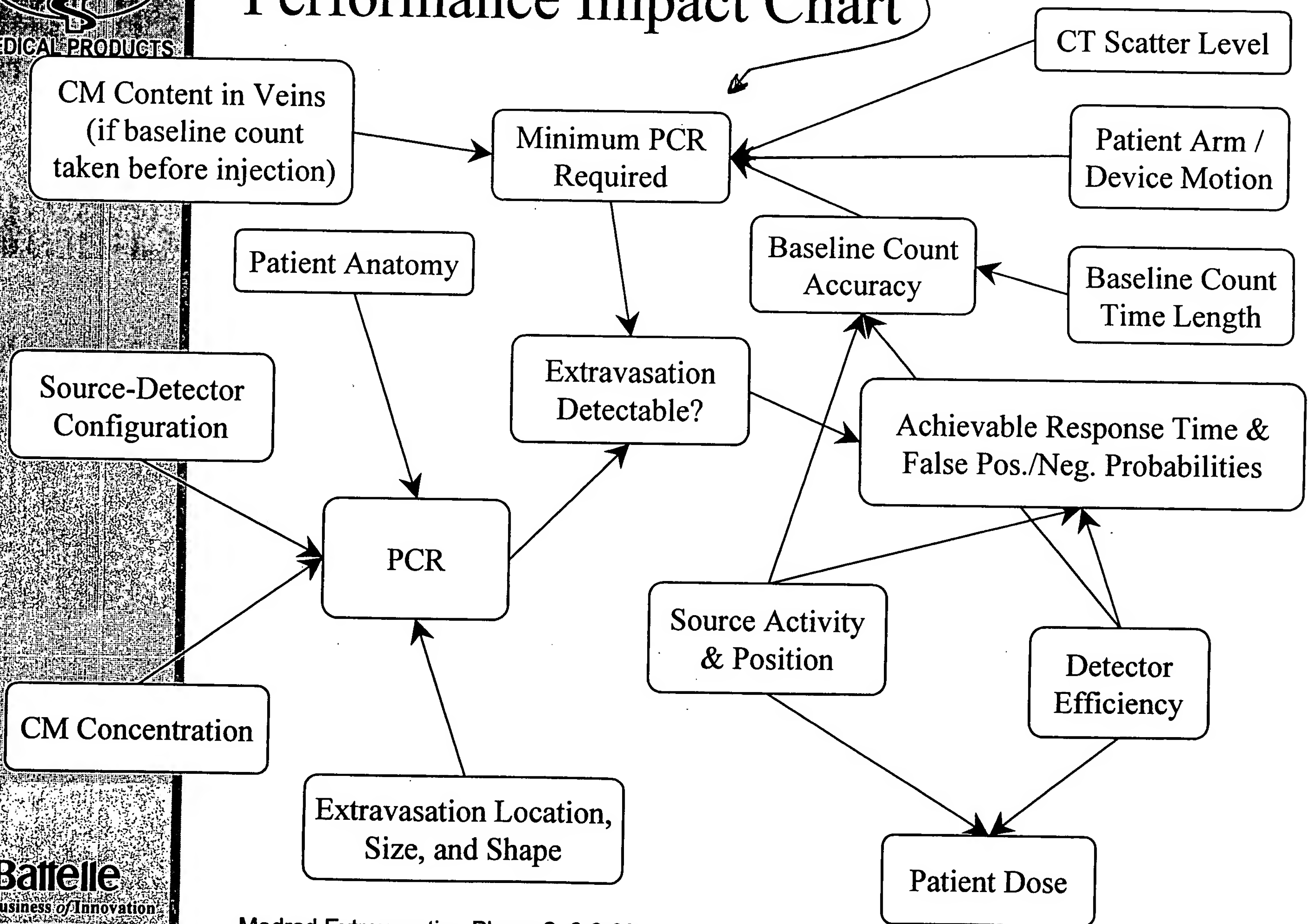
Brain CT Exam dose:	200-400 mrem
Abdominal CT:	2000 mrem
Dental x-ray:	10 mrem
Medrad Device (Calculated 20 min exp.):	0.64 mrem

Note: For a 9.5% efficient detector, multiply above doses by 10

Battelle
The Business of Innovation

Noise from outside sources

Performance Impact Chart



MEDICAL PRODUCTS

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Key Conclusions (Combining Phases 1 & 2)

- Larger detector surface area (D1+D2+D3):
  - -Often decreased PCR ("shadow") - increased PCR if more target in S-D direct path
  - -Always decreased predicted patient dose
- Single detector (D2) in conjunction with source array detected all targets (T1-T4) within PCR margin
- PCR may need to be improved in certain sub-regions

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Battelle
The Business of Innovation

Key Conclusions (Combining Phases 1 & 2)

- PCR will decrease several percentage points when lower concentration CM is used

- May be able to increase PCR significantly by using lower energy photons (I-129) with small increase to patient dose

MEDICAL PRODUCTS

Current Questions

- When should the baseline count be made relative to CM injection?
- Before injection? If so, what is the total volume and blood concentration of CM in veins located in the search region? (If large this increases PCR margin)
- What other target locations should be considered? Under/behind bone?

Suggested Future Phase Work

- Address current questions
- Develop computer model/simulation to increase PCR in certain parts of the search region
  - -Optimize source array layout and detector(s) position
  - -Optimize photon energy used
- Further investigate detector technologies
- Consider non-intrusive approaches to placing sources and detectors near search region while allowing palpitation (cradle, strap, etc.)

MEDICAL PRODUCTS

Suggested Future Phase Work (cont.)

- Develop a physical model with optimized source-detector array configuration and non-optimized signal processing algorithms for functional experiments with human phantom

- Further investigate the following by using computer model:

  Patient-device relative motion
  Patient limb motion (flexing, bending, etc.)
  Source-detector relative motion

- Obtain accurate CT scatter data or measurements for old and new generation CT scanners

Battelle
The Business of Innovation

MEDICAL PRODUCTS

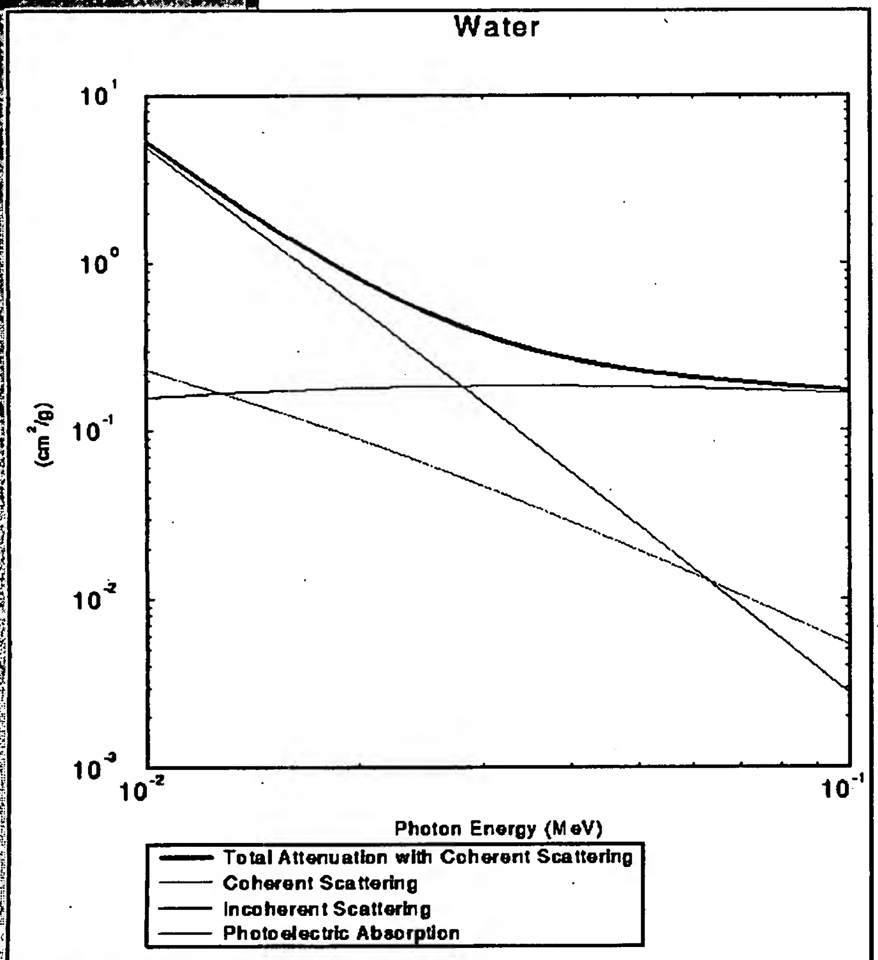
Selected Phase Work Details

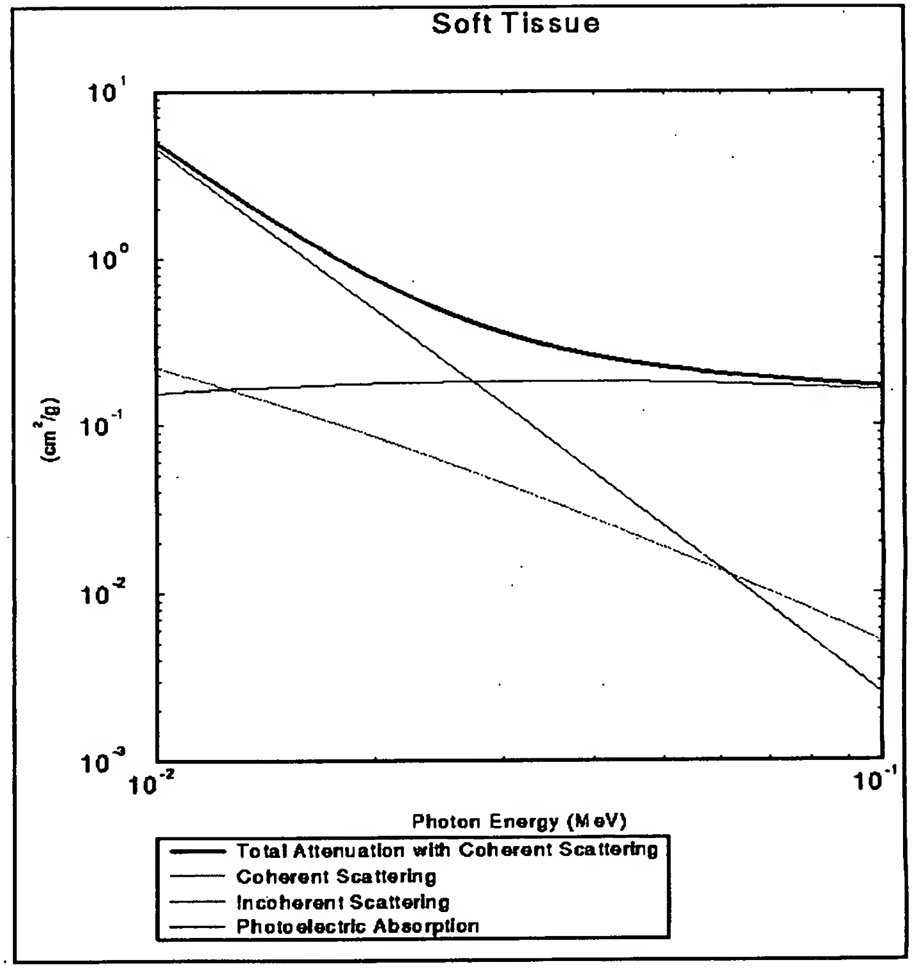
Battelle
The Business of Innovation

Alternative Detector Technologies

- Xenon (Xe) - filled tube
  - -Proportional counter
  - -More efficient than GM (Neon-Halogen)
  - -Higher voltage: Xe=1650VDC (GM=900VDC)
- Silicon (Si) diodes
  - -Only slightly more efficient than GM
  - -Inexpensive in quantity (see Appendix for details)
- Amorphous Selenium (aSe)
  - -High efficiency (possibly > 60%)
  - -Gaining popularity for digital x-rays (possibly affordable)
- Scintillating fiber: Battelle-managed Pacific Northwest National Laboratory (PNNL) - Needs more examination

Simulating Soft Tissue



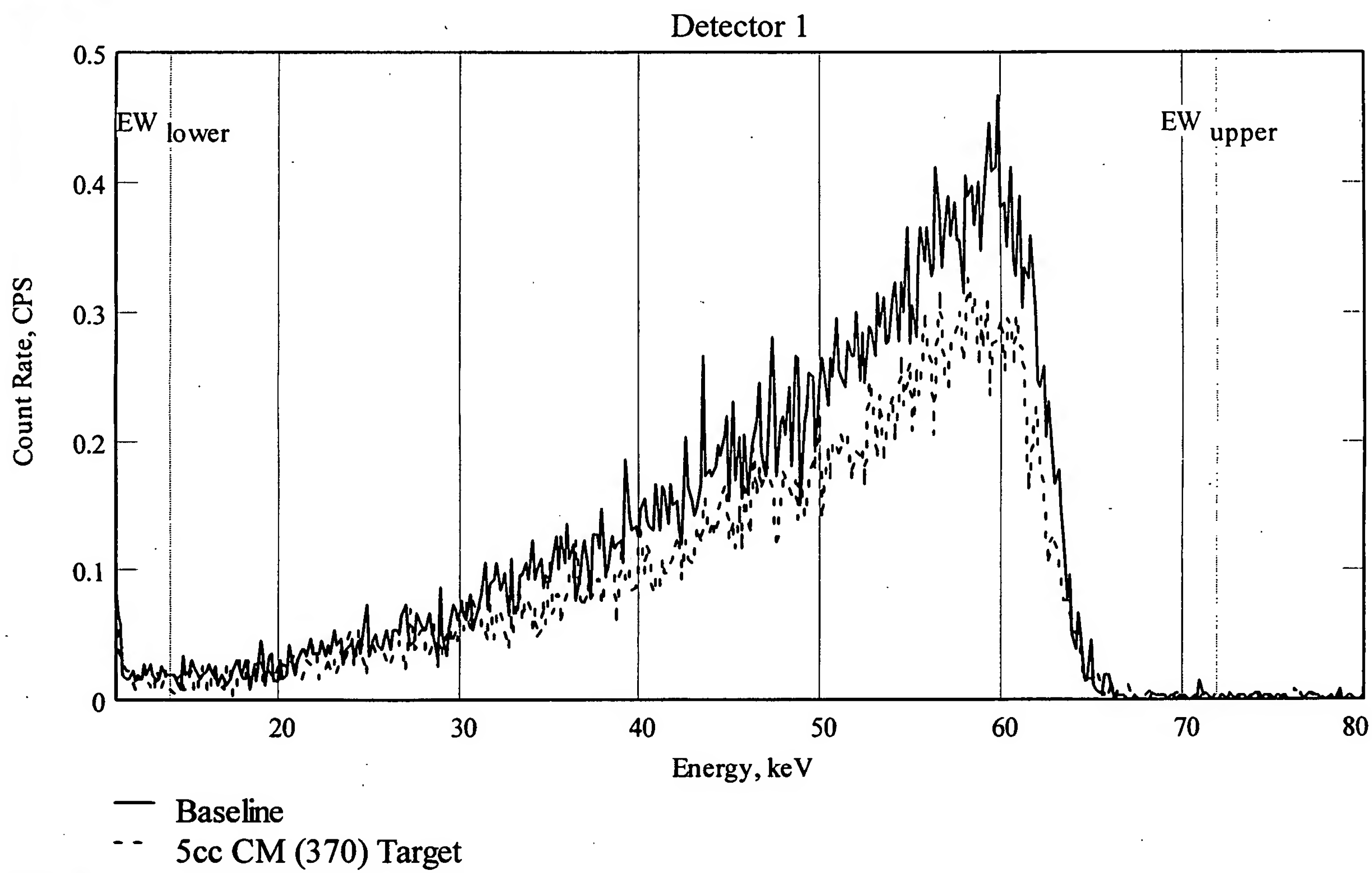


MEDICAL PRODUCTS

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Using Energy Spectral Analysis

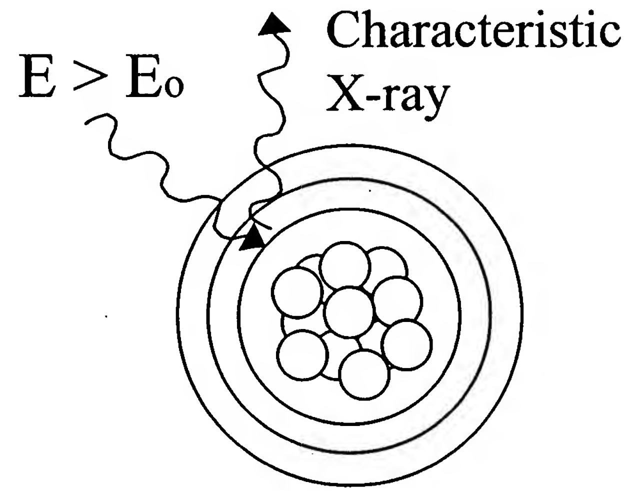


Battelle
The Business of Innovation

New Concepts for Modes of Detection

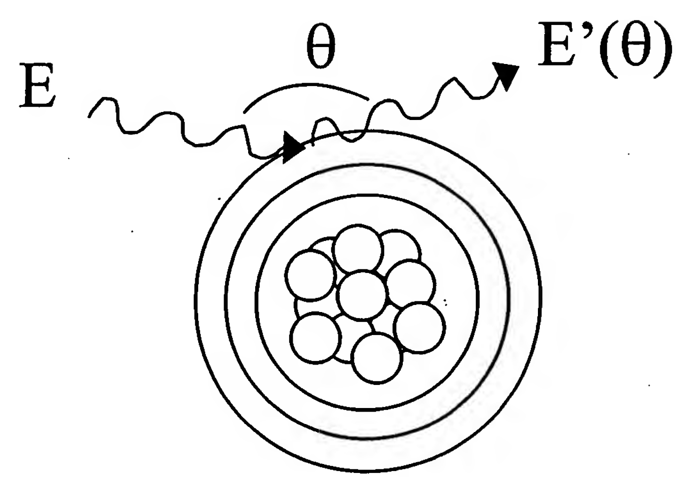
- X-ray fluorescence

  In studying iodine scattering and absorption properties, observed fluorescence at 33.17 keV - Idea: bombard with $E > E_o$ and use energy windowing to detect 33.17 keV and below



- Scatter mode

  Back = co-located S-D



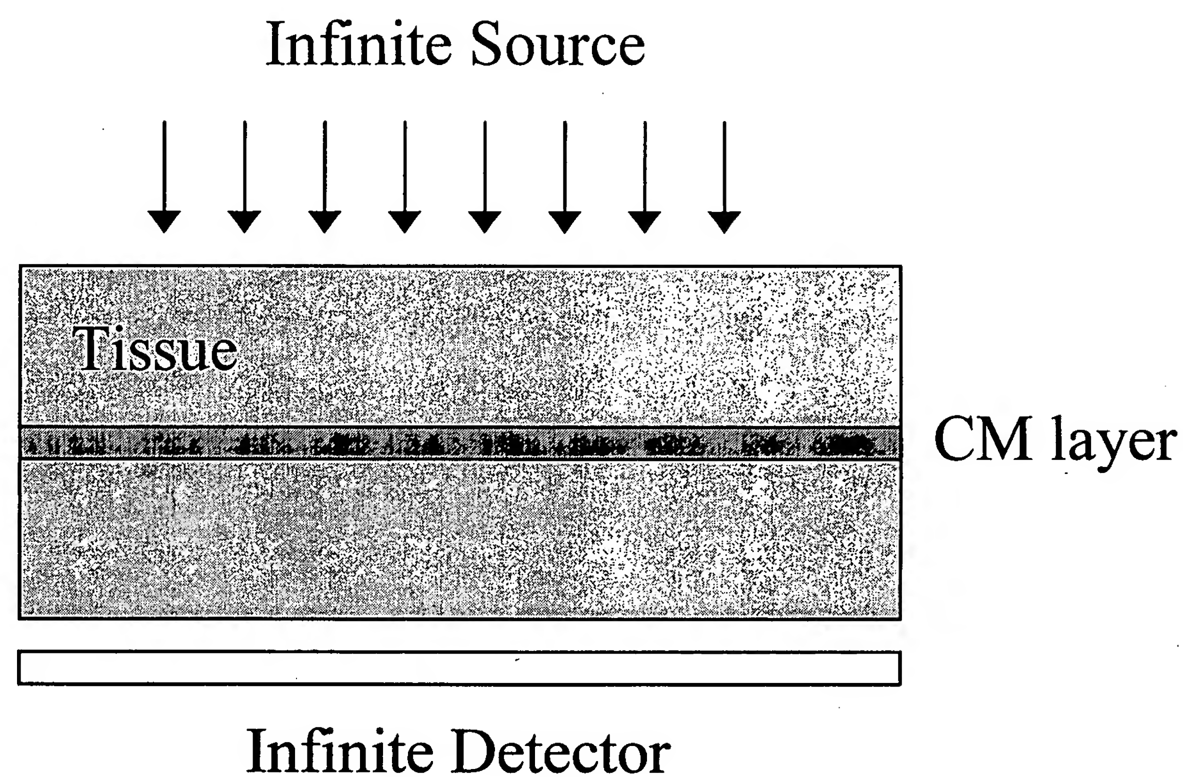
MEDICAL PRODUCTS

Superior Source: Iodine-129

- "Iodine" just coincidence
- Large jump in absorption just after fluorescence energy 33.17 keV was observed
- Created a simple model

Battelle
The Business of Innovation

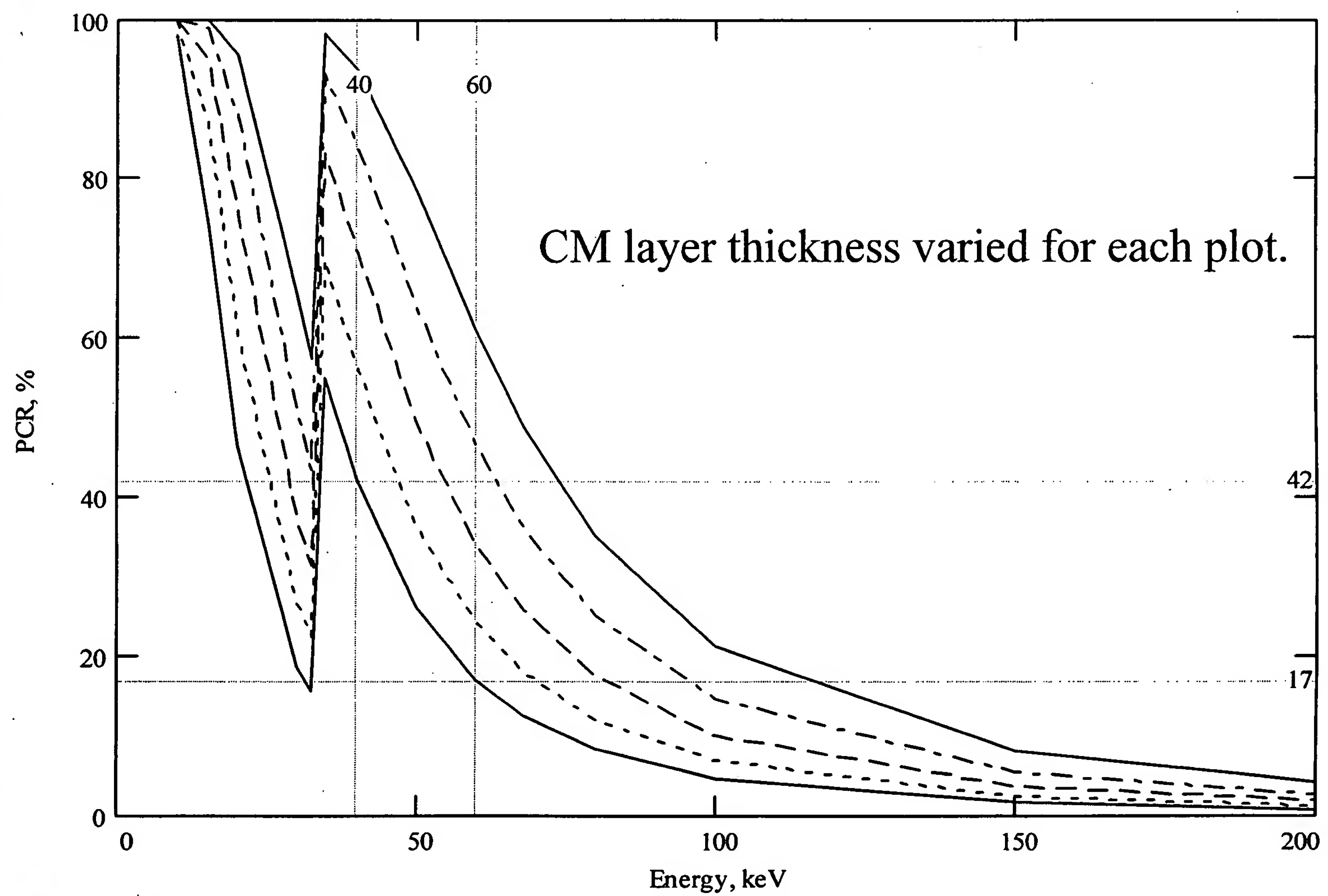
Superior Source: Iodine-129 (cont.)



MEDICAL PRODUCTS

Battelle
The Business of Innovation

Superior Source: Iodine-129 (cont.)



Superior Source: Iodine-129 (cont.)

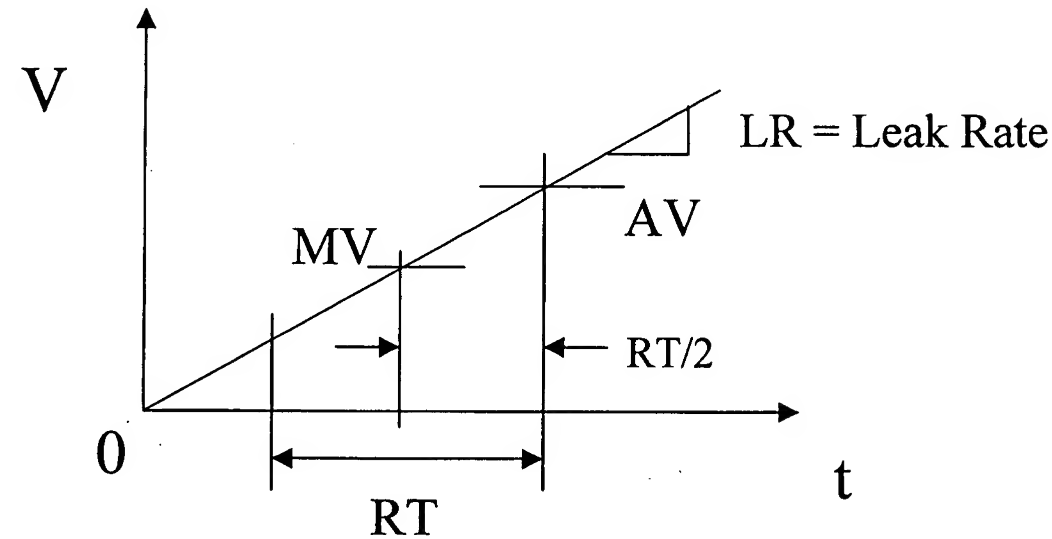
- Searched for nuclides emitting EM rays with energies > 33.17 keV and with long half-lives
- Found I-129: Photopeak = 40 keV
- May be possible to make I-129 array or planar type within desired source UMC

MEDICAL PRODUCTS

Battelle
The Business of Innovation

MEDICAL PRODUCTS

Effect of CM Leak Rate



RT = Response Time. (Algorithm lag time.)
MV = Mean Volume (Target Volume) that system and algorithm responds to.
AV = Alarm Volume. Volume reached when alarm should (with high probability) start.
AV = MV + LR*(RT/2). If MV = 5cc, LR = 2cc/sec, and RT = 2sec, then AV = 7cc. If we choose MV = 5cc, LR = 0.75cc/sec, and RT = 2 sec, then AV = 5.75cc. Let me know what you'd like.

Battelle
The Business of Innovation